Robin Sequence: From Diagnosis to Development of an Effective Management Plan

abstract

The triad of micrognathia, glossoptosis, and resultant airway obstruction is known as Robin sequence (RS). Although RS is a well-recognized clinical entity, there is wide variability in the diagnosis and care of children born with RS. Systematic evaluations of treatments and clinical outcomes for children with RS are lacking despite the advances in clinical care over the past 20 years. We explore the pathogenesis, developmental and genetic models, morphology, and syndromes and malformations associated with RS. Current classification systems for RS do not account for the heterogeneity among infants with RS, and they do not allow for prediction of the optimal management course for an individual child. Although upper airway obstruction for some infants with RS can be treated adequately with positioning, other children may require a tracheostomy. Care must be customized for each patient with RS, and health care providers must understand the anatomy and mechanism of airway obstruction to develop an individualized treatment plan to improve breathing and achieve optimal growth and development. In this article we provide a comprehensive overview of evaluation strategies and therapeutic options for children born with RS. We also propose a conceptual treatment protocol to guide the provider who is caring for a child with RS. *Pediatrics* 2011;127:936–948

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KEY WORDS

Robin sequence, micrognathia, glossoptosis, airway obstruction, management strategies

ABBREVIATIONS

RS—Robin sequence
SS—Stickler syndrome
NPA—nasopharyngeal airway
TLA—tongue-lip adhesion
MDO—mandibular distraction osteogenesis

All authors were involved with all stages of manuscript preparation, including contribution to the intellectual content, the writing process, and critical revision of all sections of the article. Dr Evans is the primary author of the article, and she composed the initial outline and draft of the article and all subsequent drafts, coordinated the writing and re-writing of individual sections of the article, drafted the submitted and revised versions of the article, created Supplemental Figure A and Figure 7, and developed Table 2. Dr Sie's input and expertise were critical in developing the "Management of RS Is Evolving" section, she specifically contributed to writing and revising the "Nonsurgical Therapies" section, and she made significant contributions to all subsections of the "Anatomic Manifestations of RS" section. Dr Hopper helped develop and revise Table 2 and made significant contributions to the "Surgical Therapies" section of the "Management of RS Is Evolving" portion of the article. Ms Glass contributed substantially to writing the "Attention to Growth, Feeding, and Reflux" section of the article and critical revision of the entire article, and provided unique and firsthand insight into the feeding challenges faced by infants and children with RS. Dr Hing contributed substantially to writing "The Genetics of RS" section of the article, provided assistance in revising the entire article, and developed Table 1. Dr Cunningham contributed substantially to the initial conception of the article, mentored and assisted Dr Evans throughout the entire writing process, critically revised all drafts of the article, and made substantial contributions to all sections of the article, including helping design the visual aspects of the article.

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Mandibular anomalies are common in neonates, and micrognathia has been described in more than 100 syndromes.[1] Although often difficult to distinguish during infancy, micrognathia is reduced mandibular size, and retrognathia is posterior mandibular positioning.[2] The triad of micrognathia (small and symmetrically receded mandible), glossoptosis (tongue that obstructs the posterior pharyngeal space), and resultant airway obstruction, described in 1923 by Pierre Robin, is known as Robin sequence (RS).[3,4] In addition to the variation in phenotypic severity of micrognathia and glossoptosis, cleft palate (U-shaped or V-shaped) occurs in up to 90% of children with RS.[5,6] Whether cleft palate is an obligatory feature of RS remains debated. A sequence is a collection of abnormalities that result from previous developmental anomalies or mechanical processes. The prevailing concept is that mandibular hypoplasia leads to the Robin phenotype. However, multiple well-defined conditions may produce a similar phenotype. Until the etiology of RS is better understood, controversy will remain over obligatory features. In this article we review what is currently known about the heterogeneous population of children with RS, defined in this article as micrognathia, glossoptosis, and airway obstruction. Our goal is to help clinicians recognize RS, understand functional and anatomic implications of RS, and become familiar with evaluation strategies and management tools used in caring for a child with RS.

A recent survey of 73 cleft and craniofacial providers yielded 14 different definitions of RS, which emphasizes the widespread variability in defining this well-known eponym.[7] The tremendous heterogeneity and lack of uniformly accepted diagnostic criteria for, or definition of, RS make it challenging to know its true incidence. Estimates of birth prevalence range from 1 in 8500 to 1 in 20 000 births.[8,9] Over the last 10 years, the mortality rate for all children with RS is estimated to have been 1.7% to 11.3% and up to 26% for children with RS with multiple malformations.[5,10–13]

Thus far, classification schemes of RS have not provided insight into etiology or prognosis. Categorizing children as having syndromic versus isolated RS is inadequate, because there is striking phenotypic heterogeneity among syndromes and anomalies associated with RS and within so-called isolated RS. Determining the degree of airway obstruction and feeding issues is essential in caring for a child born with RS. Although the concept of RS is familiar to most pediatric providers, no gold standard exists for making the diagnosis. More than 20 years ago, Shprintzen[14] suggested varying treatment according to the etiology and mechanism of airway obstruction. Because of the variety in the phenotype and natural course of RS, treatment should be tailored to the individual patient.

A HISTORICAL PERSPECTIVE

The triad of cleft palate, micrognathia, and airway obstruction was described by St Hilaire in 1822, by Fairbain in 1846, and by Shukowsky in 1911.[15] Pierre Robin, a French stomatologist, first described glossoptosis and its relationship with micrognathia and airway complications that can occur in the condition that now bears his name. In 1923, Robin described "liberation of the oral pharynx" with a prosthetic device that pulled the jaw and tongue forward.[3,4] He later reported growth failure and death caused by the respiratory complications that occur with micrognathia and glossoptosis.[16] Supplemental Figure A summarizes significant milestones that have shaped our understanding and management of children born with RS.

EMBRYONIC ORIGINS OF THE ROBIN PHENOTYPE

The primary pathogenetic event that leads to RS is unknown. Micrognathia causing upward and posterior displacement of the tongue, preventing closure of the palatine shelves before the 10th week of gestation, is the accepted dogma. In animal models, intrinsic and extrinsic factors that affect mandibular development have been hypothesized to cause RS.[17,18] For instance, results of research on oligohydramnios-induced intrauterine growth restriction support the constricted mandible as a primary mechanical event that can lead to palatal clefting in rats.[19] In mice with *COL2A1* (collagen, type II, α-1) mutations, detection of mandibular hypoplasia before closure of the palatal shelves suggests a relationship between the two; in these mutants the gene may play a role in 2 independent embryologic events: mandibular development and palate fusion (a maxillary defect) that may be independent of tongue position.[20] Hanson and Smith[21] proposed that the palatal cleft shape provides a clue to the morphogenesis of RS and suggests that when the defect in palate closure is a result of mechanical obstruction by the tongue, rather than intrinsic failure of anterior-to-posterior fusion of the palatal shelves, a U-shaped cleft results (Fig 1). In addition, perturbation of both transcription factors and regulatory enhancers (Dlx5/6, Hand2, and Mef2c) that play a role in neural crest patterning and signaling leads to a Robin phenotype in mice, which suggests multiple potential developmental targets.[22,23] The clinical importance of RS will undoubtedly drive future molecular genetic studies to identify its pathogenesis.

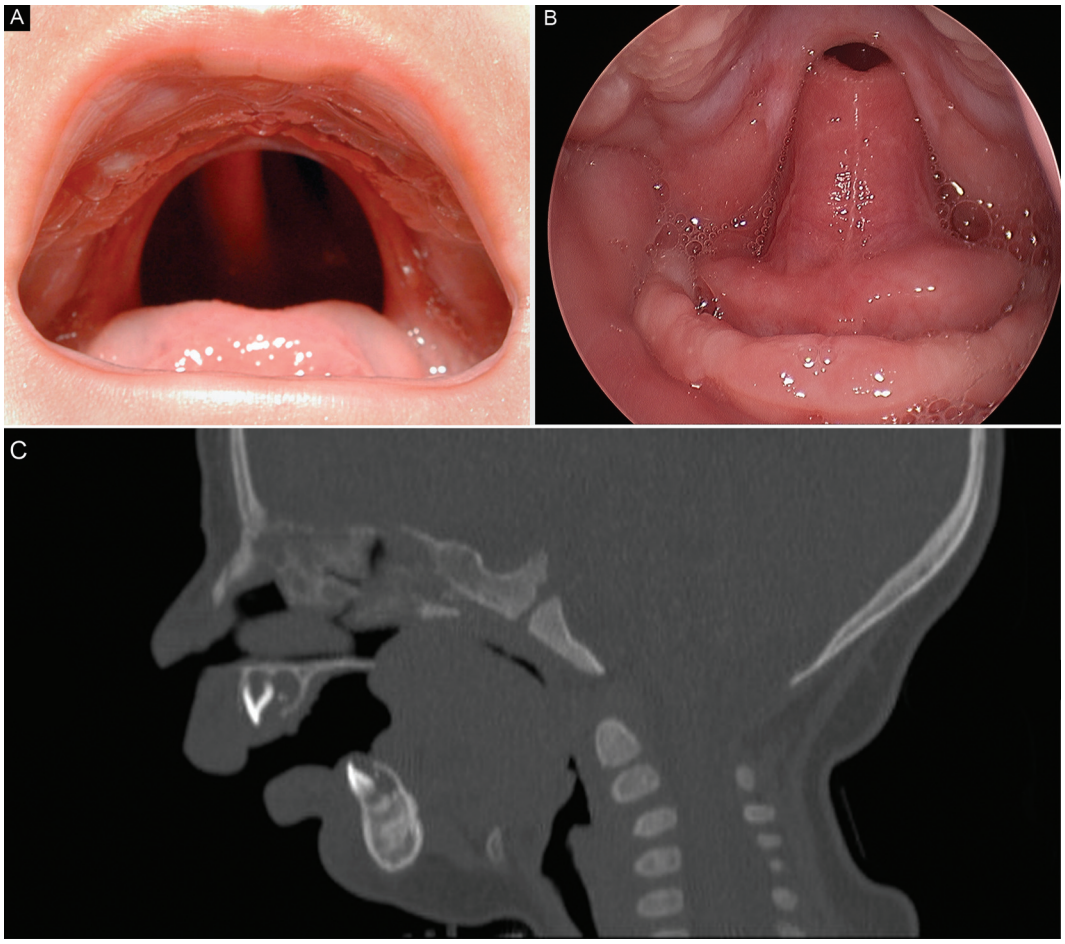

FIGURE 1
A, U-shaped cleft palate. B, Endoscopy captured this intraoral view of glossoptosis; the tongue is actually pulled back into the cleft palate so that only the undersurface of the tongue is visible. (Image courtesy of Dr Jonathan Perkins, Division of Pediatric Otolaryngology, Department of Otolaryngology Head and Neck Surgery.) C, Computed-tomography scan sagittal view of posterior tongue occluding the pharyngeal airway in an infant with RS.

THE GENETICS OF RS

More than half of the infants born with RS will have an associated syndrome, chromosomal abnormality, additional anomalies, or other medical concerns.[10,24,25] Thus, a genetic evaluation should be considered for infants with RS to identify a specific syndromic diagnosis and provide recommendations for genetic testing.

Associated Syndromes

More than 40 syndromes with RS have been described,[2,26] the most common of which are Stickler syndrome (SS) and 22q11.2 deletion syndrome (Table 1). Between 11% and 18% of people with RS will have SS.[9,10,13,24] SS is a connective tissue disorder with characteristic ocular (congenital high myopia, vitreous anomaly, risk of retinal detachment, cataracts), orofacial (RS, midface hypoplasia, depressed nasal bridge, anteverted nares), auditory (sensorineural or conductive hearing loss), and articular (joint hypermobility, spondyloepiphyseal dysplasia, precocious osteoarthritis) manifestations. The autosomal dominant forms of SS are divided into 3 types (types 1 and 2 have ocular findings). Type 1, caused by mutations in *COL2A1*, is most frequent and accounts for more than 80% of cases of SS.[27] Mutations in *COL11A1* are found in people with type 2 SS, and mutations in *COL11A2* have been noted in those with nonocular type 3 SS. *COL9A1* gene mutations have been observed in a rare autosomal recessive form of SS. Clinical testing is available for all 4 genes.

Because SS is a leading cause of retinal detachment and blindness in children,[28] all infants with RS should have an initial ophthalmology evaluation between 6 and 12 months of age or at the time of definitive molecular diagnosis of SS and routine surveillance thereafter. Because normal newborns are hyperopic, any degree of myopia with the presence of characteristic RS facial features should raise suspicion for SS. In early infancy, differentiating iso-

TABLE 1 Conditions Associated With RS

Condition	OMIM Classification No.
Most common	
SS	108300, 604841, 184840
Chromosome 22q11 deletion syndrome	192430
Less common	
Skeletal dysplasias	
Spondyloepiphyseal dysplasia congenita	183900
Kniest dysplasia	156550
Diastrophic dysplasia	222600
Campomelic dysplasia	114290
Osteopathia striata with cranial sclerosis	300373
Marshall syndrome	154780
Otopalatodigital syndrome type II	304120
Dysmorphic monogenic conditions	
Treacher Collins syndrome	154500
Nager syndrome	154400
Miller syndrome	—
Catel-Manzke syndrome	302380
Cerebrocostomandibular syndrome	117650
Cerebrocostomandibular-like syndrome (congenital disorder of glycosylation type IIg)	611209
Kabuki syndrome	147920
Toriello-Carey syndrome	217980
Neurologic conditions	
Congenital myotonic dystrophy	—
Carey-Fineman-Ziter syndrome	254940
Chromosomal abnormalities	
Chromosome 4q32-qter deletion	—
Chromosome 2q24-q33 deletion	—
Chromosome 11q21-q23 duplication	—
Chromosome 17q21 deletion/translocation near SOX9	—
Intrauterine exposures	
Fetal alcohol syndrome	—
Maternal diabetes	—
Miscellaneous	
TARP syndrome (talipes, atrial septal defect, RS, and persistent superior vena cava)	311900
RS with cleft mandible and limb anomalies	268305
Distal arthrogryposis-RS	208155

OMIM indicates Online Mendelian Inheritance in Man (available at www.ncbi.nlm.nih.gov/omim).[26]

lated RS from common syndromes associated with RS is difficult. Even with ophthalmologic screening, it is important to consider molecular testing (including SS-associated collagen gene analysis and fluorescence in situ hybridization for 22q11.2 deletion syndrome).

Isolated RS and Cytogenetic Changes

A family history of clefting and/or micrognathia has been reported in a significant subset of children with isolated RS, but for most, the genetic cause is not known.[10] Marques et al[29] studied 36 children with isolated RS without SS and detected a family history of clefting in 27.7% of them, which suggests a role for heredity in the etiopathogenesis of RS. Jakobsen et al[30] pursued a search of Medline and the Human Cytogenetic Database to identify putative RS candidate gene loci. They identified 4 candidate loci (2q, 4q, 11q, and 17q) for which at least 2 patients with RS had a deletion/duplication/translocation, which supports a genetic basis for RS.

PRENATAL DIAGNOSIS IS CHALLENGING

There have been few reports on prenatal diagnosis of RS. Antenatal recognition allows immediate intervention at birth to prevent life-threatening airway obstruction. Prenatal suspicion of RS relies on subjective ultrasound identification of micrognathia (a prominent upper lip and small chin in the facial profile). Micrognathia is often missed on two-dimensional screening ultrasound.[31] Such diagnosis is also complicated in that retrognathia is a normal finding in early gestation; the mandible may undergo significant growth after 20 weeks' gestation and after birth.[32] Reevaluating the fetal mandible in the third trimester more accurately demonstrates mandibular size and form. Results of 1 retrospective study suggested that antenatal sonographic visualization of glossoptosis is possible; however, it was limited to 4 cases of RS.[33]

Authors of retrospective studies have described objective modalities for monitoring jaw growth and detection of micrognathia and retrognathia with two- and three-dimensional prenatal ultrasound.[34–40] Paladini et al[41] developed a mandibular growth chart for the fetal mandible relative to biparietal diameter and proposed the jaw index as a more sensitive and specific mode of identifying micrognathia. However, these calculations are not routinely used. Three-dimensional ultrasound that uses multiplanar navigation may improve visualization of facial morphology and micrognathia; however, three-dimensional ultrasound is not yet standard in prenatal imaging, and diagnostic criteria have not yet been established.[42,43]Although knowledge about normal fetal mandibular growth patterns and ultrasound technology are improving, reliable prenatal detection of micrognathia (and RS) depends on standardization of tools and appropriate timing of mandibular evaluation.

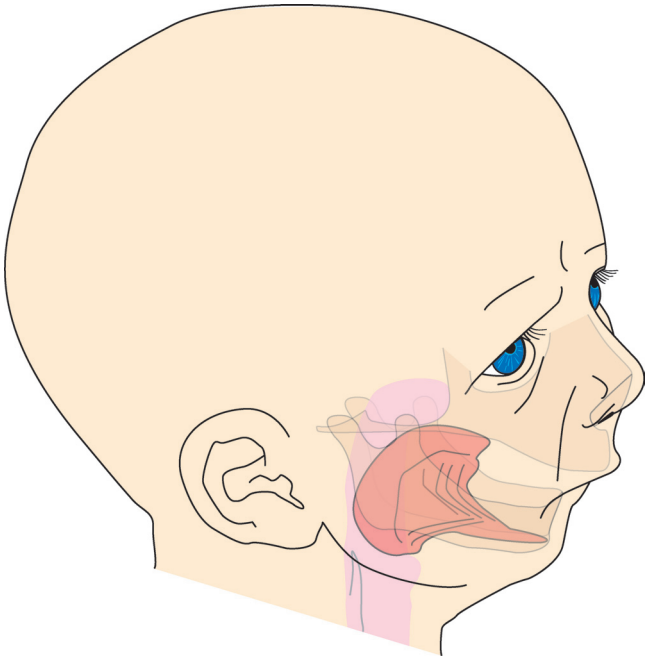

FIGURE 2
Illustration of the skeletal, soft tissue, and airway relationships in an infant with RS. Significant mandibular hypoplasia, glossoptosis, and a narrowed airway. (Illustration by Eden Palmer.)

ANATOMIC MANIFESTATIONS OF RS

Mechanism of Airway Obstruction

Airway obstruction in RS was initially thought to be caused exclusively by displacement of the tongue into the hypopharynx, thus occluding the airway at the level of the epiglottis[3,4] (Fig 2). Alternative proposed mechanisms of airway obstruction in patients with RS include disproportionate tongue growth, tongue prolapse into the cleft palate, lack of voluntary control of tongue musculature, and negative pressure pull of the tongue into the hypopharynx.[44] Abnormal maxillary morphology causing midface hypoplasia has also been described with RS and may contribute to airway obstruction, particularly in those with SS.[45,46]

Most otolaryngologists and pulmonologists agree that upper airway obstruction at the tongue base caused by glossoptosis is a defining feature of the RS phenotype (Fig 1B). Sher et al[47,48] endoscopically classified 4 types of airway obstruction in 33 children with craniofacial anomalies and subsequently applied them to children with RS. Type 1 obstruction is posterior movement of the dorsal tongue against the pharyngeal wall. Marques et al[11] reported that of 62 children with probable isolated RS evaluated by nasopharyngoscopy, 90.9% were classified as having type 1 obstruction, 75% of whom responded to nonsurgical management.

Morphometry of Mandibular Growth

Airway obstruction in infants with RS commonly improves with time. Is this because the mandible grows more in the postnatal period or because glossoptosis improves with growth and neurologic development?[49] Many modalities to objectify micrognathia and glossoptosis have been used; however, few apply to neonates and infants, and none has been universally adopted.[50,51] Pruzansky and Richmond[52] used cephalograms (lateral radiographs that illustrate the facial profile, mandibular length, and distance between the upper and lower alveoli[53,54]) to analyze mandibular form and growth in children with micrognathia. He postulated that the mandible possesses significant potential for growth in children with RS.[55] Analyzing cephalograms, Figueroa et al[56] uncovered differences in mandibular morphology, airway diameter, and mandibular growth in children with RS compared with controls with cleft palate only and no cleft, which suggests that clinical resolution of airway obstruction over the first year of life is related to accelerated mandibular growth. After using similar measures and control groups, persistence of the small mandible has also been described.[57,58] Although controversial, mandibular catch-up growth likely correlates with the etiology of the sequence or underlying syndrome.[14,59] Studies of the craniofacial skeleton of subjects with RS have uncovered more than mandibular involvement.[60] Maxillary hypoplasia has also been well described in children with RS, which supports a role for primary and persistent dysgenesis of both jaws. More recently, three-dimensional data from digital surface photogrammetry have been used to investigate craniofacial morphology.[61] Measurement of the maxillary-mandibular discrepancy on physical examination is a simple, objective measure used to quantify the small or posteriorly displaced jaw and monitor alveolar relationship after interventions and over time, but this must be done in the context of maxillary development[62] (Fig 3).

Clinical Correlation: Careful Airway Evaluation

Understanding the site of airway obstruction in RS is critical for determining optimal therapy. A thorough endoscopic airway evaluation, to best determine the level of airway obstruction, is recommended before any inter-

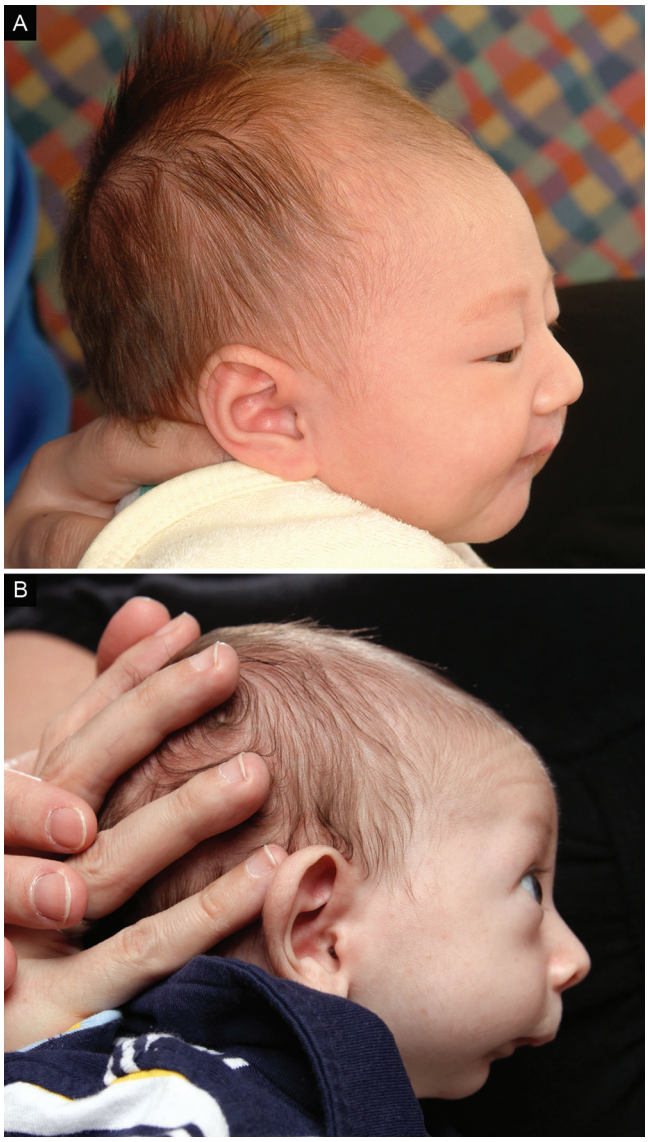

FIGURE 3
The faces of RS. A, An infant with RS and mild mandibular hypoplasia. B, An infant with RS and more significant mandibular and maxillary hypoplasia and notable alveolar discrepancy.

vention. Dynamic assessment of the upper airway and vocal cord mobility can be achieved with bedside laryngoscopy. Direct laryngoscopy and bronchoscopy are necessary to evaluate subglottic structures, including the trachea and bronchi, although with severe micrognathia, it may not be possible. A jaw-thrust maneuver performed under anesthesia, in which the mandible is brought forward manually with direct endoscopic visualization, can predict dynamic airway change that occurs with mandibular advancement.

MANAGEMENT OF RS IS EVOLVING

Nonsurgical Therapies

Infants with RS face 2 main problems: upper airway obstruction and feeding difficulties. Without treatment, children with RS and significant airway obstruction may succumb to asphyxia, hypoxia, respiratory failure, cor pulmonale, malnutrition, and death. The first priority of treatment for RS addresses the airway. Meyer et al[63] reported success with nonsurgical airway intervention in 70% of infants with isolated RS.

The first-line management is prone positioning. Placing the infant prone will allow the mandible and tongue to fall forward and reduce airway obstruction at the tongue-base level. Positioning alone is successful for at least half of all children with RS.[5,24,63,64] However, ongoing monitoring of breathing, feeding, and growth is critical, because significant airway obstruction may present after the newborn period. Airway obstruction can occur spontaneously, with feeding or sleep, and progressive airway obstruction may become more noticeable in the second month of life. Monitoring for CO_2 retention by measuring serum electrolyte levels is appropriate for patients with RS whose condition is not critical.

Using modified polysomnography, Bull et al[65] concluded that monitoring for CO_2 retention in addition to hypoxemia or desaturation is important in early infancy. Although noninvasive modalities that can identify and determine airway obstruction severity in RS, such as polysomnography, have been used for more than 20 years, the types of evaluations and interpretation of results vary.[66–69] Overnight polysomnography with multiple measures of airflow may have a role in quantifying more subtle airway obstruction, particularly if the clinical picture is not clear.

When positioning alone fails, tongue-base airway obstruction may be relieved by placement of a nasopharyngeal airway (NPA) without anesthesia. The distal end of a modified endotracheal tube is placed intranasally and positioned in the distal oropharynx, beyond the area of glossoptosis. Placing the endoscope within the nasopharyngeal tube allows direct visualization

FIGURE 4
An NPA in an infant with RS.

and position verification, and the proximal end of the NPA is secured[70] (Fig 4). Obstruction may be relieved as the NPA breaks the seal between the tongue and posterior pharynx, and the child can breathe through the tube and contralateral nostril.

Relief of airway obstruction, normalization of oxygen saturations, and weight gain have been well described with NPA use in hospitalized infants with RS.[70,71] Transitioning home with a stable NPA in place is possible when parents become comfortable with tube care and equipment. Discharge from the hospital with an NPA is now viewed as a safe and effective option for infants with RS in many institutions.[72,73]

Surgical Therapies

Persistent airway obstruction despite prone positioning or NPA use is an indication to explore surgical interventions[63] (Fig 5). Before considering more invasive measures, evaluation of the distal airway or central respiratory drive may help uncover additional etiologies of respiratory insufficiency. Airway compromise caused by hypotonia, central apnea, laryngomalacia, tracheomalacia, and bronchial stenosis are not common but have been described in patients with RS.[74] The level of airway obstruction or presence of multiple levels of airway narrowing, demonstrated clinically and endoscopically, should guide the intervention. Surgical procedures used for patients with RS include tongue-lip adhesion (TLA), mandibular distraction osteogenesis (MDO), and tracheotomy (Table 2). Different institutions may have varying levels of expertise with various procedures.

Tongue-Lip Adhesion

Glossopexy (by means of TLA) can be effective in relieving tongue-base obstruction. The anterior ventral tongue is anchored to the lower lip (mucosa plus or minus muscle), and the posterior tongue is anchored to the mandible. Adverse outcomes include dehiscence and need for subsequent procedures.[75] There is disagreement about feeding outcomes with TLA; some argue that it is detrimental for feeding because it alters tongue mobility and swallowing, and others have found improved feeding and weight gain after glossopexy.[74,76] Kirschner et al[64] have recommended TLA as a first-line intervention for tongue-base obstruction when positioning fails.

Mandibular Distraction Osteogenesis

Patients with 1 level of airway obstruction at the tongue-base may be candidates for MDO, a technique that increases pharyngeal airway size by gradual mandibular lengthening. The procedure includes bilateral osteotomies and placement of distraction devices, which can be internal or external with percutaneous pins. External devices are easy to adjust and remove

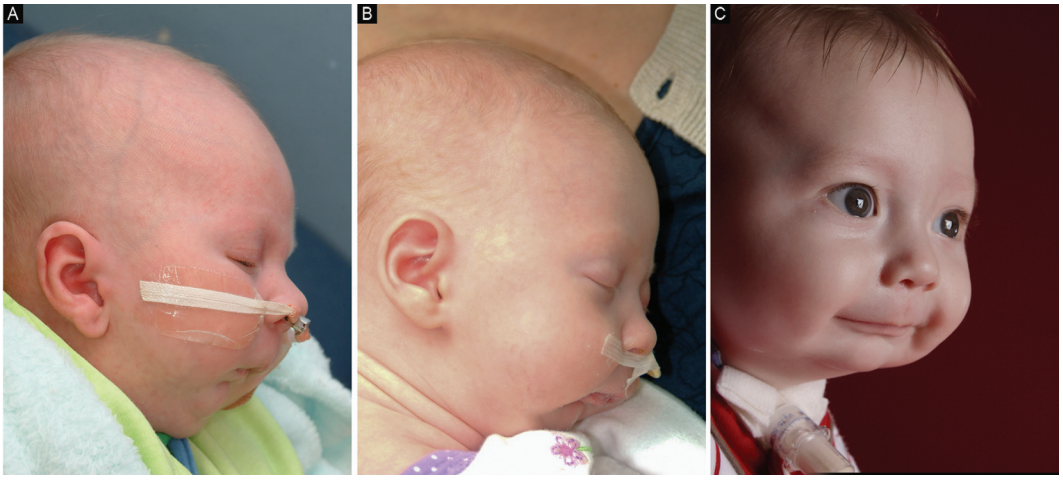

FIGURE 5
Presurgical photographs of 3 infants with RS who all failed prone positioning and ultimately underwent MDO in the first year of life. A, Prior management with an NPA (an NPA is in place in this photograph). B, Neonatal distraction. C, Initial management with tracheotomy and later MDO.

TABLE 2 Management of Airway Obstruction in RS

	Reported Frequency of Success, %[a]	Possible Indications	Potential Adverse Effects
Nonsurgical			
Positioning	49–77[5,24,63,64]	Mild, intermittent airway obstruction	None
NPA	36–100[24,63,71,73]	Single level of airway obstruction at tongue base	Nasal stenosis; positional; occlusion
Endotracheal intubation	43[24]	Temporary airway stabilization	Minimal in the short-term
Surgical			
TLA	33–100[24,48,62,64,74,76,102]	Single level of airway obstruction at tongue base not responsive to nonsurgical interventions	Feeding issues; dehiscence of adhesion; injury of salivary structures; minimal long-term effects on speech production and development; speech issues with late release
MDO	88–100[81,82,103]	Single level of airway obstruction at tongue base not responsive to nonsurgical interventions	Disruption of permanent teeth; dislodgement or failure of appliance; premature consolidation; nerve injury (inferior alveolar, marginal mandibular); pin-site/wound infection; scarring; bony malunion
Tracheotomy	5–22[13,24,74,b]	Definitive airway treatment option if >1 level of obstruction exists or if not a candidate for other interventions	Air leak (pneumomediastinum); tracheitis; bleeding; obstruction; stomal granulation; accidental decannulation; tracheomalacia; subglottic stenosis

[a] Use caution when comparing groups as different inclusion criteria.

[b] Ultimately required tracheotomy. The proportion of those whose airway obstruction resolved with tracheostomy is assumed to be ~100%.

but can be dislodged and are associated with scarring. Internal devices are usually better tolerated but require repeat dissection for removal under general anesthesia. There are 3 phases that follow the osteotomies: latency (early osteotomy healing); activation (the device opens the osteotomy at a rate of 1 to 2 mm/day [depending on age] as the mandible, suprahyoid muscles, and tongue are brought forward); and consolidation (ossification of the distracted gap with the device in place) (Fig 6). Although it does not replace the eventual need for orthognathic surgery in the future, the benefit of neonatal skeletal manipulation is derived from changing the floor-of-mouth and tongue-mandibular attachments, thereby increasing airway patency as glossoptosis is decreased.

Different objective measures have captured MDO-induced skeletal and soft tissue changes. In 1 study, cephalometric analysis before and after mandibular distraction for congenital micrognathia revealed normalization of maxillary-mandibular relationship and a mean increase in the cross-sectional airway area of 67.5%.[77] A recent study revealed a 3- to 20-fold increase in the distance from the postpharyngeal wall to the lingual root in lateral cephalograms before and after MDO.[78] Correlating these objective measures with functional outcomes, specifically in RS, has not been adequate. Computed tomography airway analysis revealed a >200% increase in the cross-sectional area of the retroglossal oropharynx correlated with an improvement in apnea-hypopnea index by polysomnography in 13 children.[79] Results of three-dimensional computed-tomography analysis have suggested that increased mandibular length and volume are reasons for airway improvement in children who undergo MDO.[80] The impact of MDO on mandibular

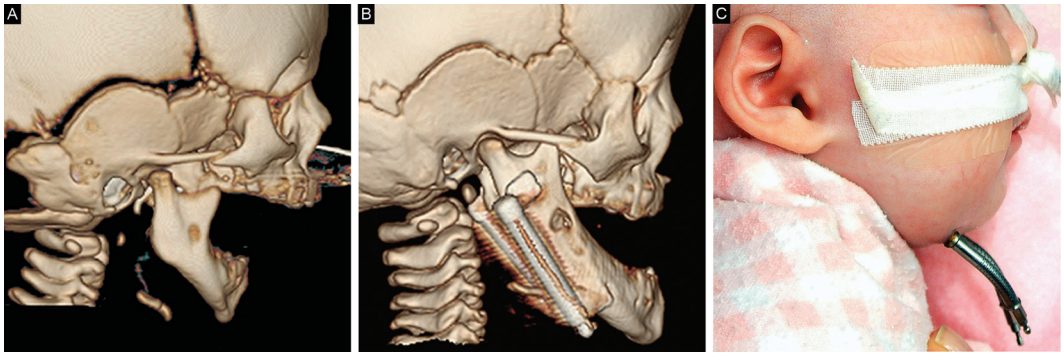

FIGURE 6

MDO in an infant with RS. A, Three-dimensional scan of the face and mandible before MDO. B, Mandible after consolidation. C, An infant during the activation phase of distraction (with a buried or internal device). Note that the activation pins are externally visible.

growth has yet to be elucidated, because it is a relatively new procedure in infants and young children; however, overcorrection of mandibular position is currently recommended to maximize airway size.[81] A meta-analysis of MDO revealed that of 92 infants who underwent distraction for mandibular hypoplasia (many diagnoses including RS), 5.3% ultimately underwent tracheostomy for respiratory distress.[82] Although results from small series of infants with RS who have successfully undergone MDO for airway obstruction in infancy exist, data from large studies analyzing outcomes have not been reported to date.[66,78,81,83,84] Although MDO is an attractive surgical option for achieving rapid resolution of airway obstruction, as with any procedure, potential risks must be considered (Table 2).

Tracheotomy

Tracheotomy is the definitive procedure for airway management for children with upper airway obstruction. It is often reserved for patients whose condition fails to respond to other measures, although it is still used as the main surgical option for children with RS and airway obstruction at some institutions. For children with multilevel airway obstruction, and particularly for patients with lower airway disease who require chronic ventilatory support, tracheotomy may be the only option.[85] Tracheostomy is associated with frequent and serious adverse effects, complications, and even death.[86,87] Although improved over the last 20 years, the morbidity and mortality associated with tracheostomy are real. A survey of parents of children with RS evaluated perceptions of quality of life and morbidity related to tracheostomy. Airway problems after decannulation, underestimation of tracheostomy duration, and frequent hospitalizations were recurring concerns; however, more than 70% of them stated that difficulties with tracheostomy met their expectations related to preoperative counseling.[88] It remains critically important to consider implications for the child, family, and home care for children with a tracheostomy.

With continued advances in imaging, accurate airway analysis, and correlation with functional outcomes and quality of life, procedures used to treat RS will continue to be refined.

ATTENTION TO GROWTH, FEEDING, AND REFLUX

Airway obstruction is the main cause of feeding and growth issues in infants with RS. It is important to distinguish between breathing-related feeding and growing issues and swallowing dysfunction, aspiration, and gastroesophageal reflux, which may negatively affect oral feeding. To further complicate the situation, some children with RS may have feeding and growth issues related to their underlying syndrome or other anomalies.

Energy Expenditures and Nutrition

In addition to feeding mechanics, it is important to consider the energy needs of infants with RS, who have increased energy expenditures because of the increased work of breathing and feeding challenges related to swallowing differences. Mild airway obstruction is not always obvious; metabolic rates may be elevated without significant airway symptoms. A recent study revealed that weight gain and severity of airway obstruction reliably predict length of stay in infants hospitalized with isolated RS, which suggests the importance of feeding and growth in risk stratification.[89] Close nutritional follow-up by a dietitian or provider with expertise in this area is critical for detecting early growth failure and optimizing nutritional status. Although early airway intervention was associated with decreased need for gastrostomy tube placement in 1 study, feeding issues or weight loss as an indication for surgical airway intervention have not been universally accepted.[90]

Feeding and Swallowing Challenges

Of infants with RS, 38% to 62% have significant feeding issues and require tube feeding, which is typically initiated with temporary supplemental nasogastric tube feeds[24,91,92]; however, of those with isolated RS, feeding issues rarely extend beyond 1 year of age.[13] Multiple studies have revealed that the incidence of chronic feeding difficulties and occurrence of gastrostomy tube placement in patients with RS is higher in RS associated with syndromes, other malformations, and neurologic abnormalities.[12,13,74,90] A study of 35 infants revealed that 40% ultimately needed tube feeding after placement of an NPA, which suggests that airway interventions may negatively affect feeding performance.[70]

Reflux

Contribution of the infant's breathing pattern to feeding issues needs to be considered. Tachypnea and increased work of breathing negatively affect coordination of sucking, swallowing, and breathing. Infants with RS may aspirate as a result of discoordination of sucking, swallowing, and breathing or primary swallowing dysfunction. Specialized feeding therapists are valuable in delineating these feeding problems. Oral and esophageal motor differences, seen with manometry and video endoscopy, can further complicate feeding.[12,69,74,93] Gastroesophageal reflux (GER) can affect the feeding-respiratory balance by causing airway inflammation and edema, increasing secretion production, and compromising swallowing mechanisms. Making the clinical diagnosis of GER can be challenging in infants with RS; however, pH-probe studies have confirmed a

higher incidence of GER in this population.[94–96] Empiric reflux treatment may improve both breathing and feeding.

Therapeutic Interventions

The initial step is finding a feeding strategy that is safe and can be implemented by the care provider or parent. Decreasing feeding duration and increasing caloric intake are possible with therapeutic oral motor techniques, positioning, and specialized bottles (squeeze bottles if there is a soft-palate cleft).[97] When feeding difficulties are not amenable to these measures, the clinician must decide whether a nasogastric tube is needed. Gastrostomy tube placement may improve oral feeding for some children. Maintaining adequate respiratory stability during feeding is a priority. Future research on the effect of early airway intervention on growth and feeding will help prioritize treatment options.

LONGITUDINAL CARE

Children with RS have a chronic condition. After infancy, management should be focused on growth, development, speech, and orthodontic care. For children with class II malocclusion (bottom teeth behind upper teeth) surgical jaw advancement at skeletal maturity may improve dental occlusion and appearance. Cognitive development, speech (velopharyngeal inadequacy), obstructive sleep apnea, and recurrence risk are key issues to be monitored by the pediatrician caring for a growing child with RS.[5,98,99] With appropriate interventions and treatment, the prognosis for children with RS is usually quite good.

CONCLUSIONS AND OFFERING

A child with RS should be cared for by a multidisciplinary team to generate the optimal treatment plan. The pediatrician will recognize the features and first clues to the phenotype and begin to evaluate the child for airway obstruction and feeding challenges and observe for any additional anomalies. Now familiar with the evaluation and management strategies for RS, the pediatrician can initiate a therapeutic plan and refer to a craniofacial team.

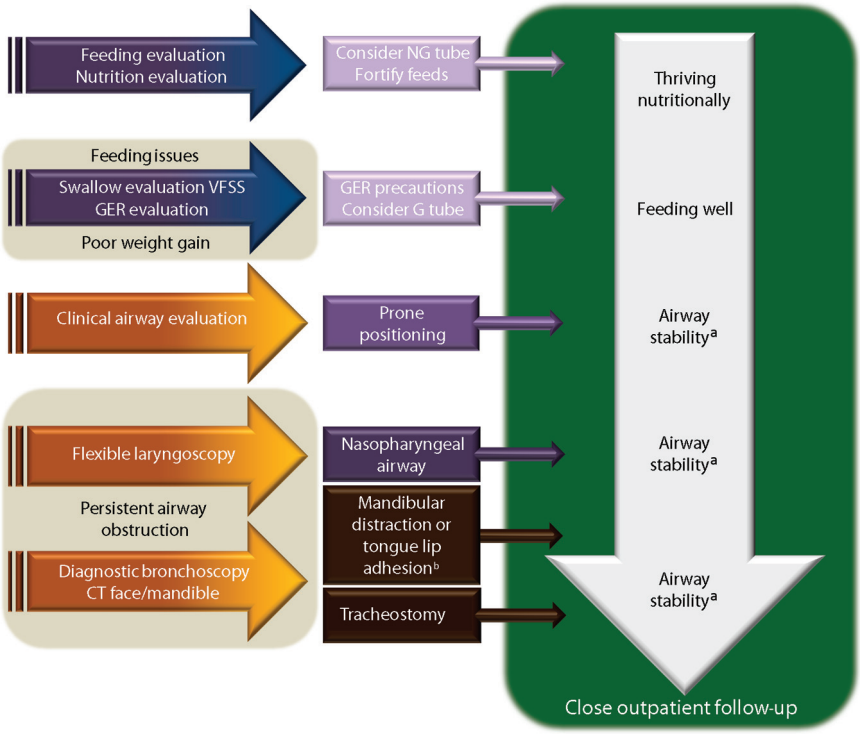

FIGURE 7
Protocol outlining clinical evaluation and medical and surgical management of RS related to airway obstruction. [a] Airway stability is defined as normal oxygen saturations, normal carbon dioxide level, and absence of work of breathing or signs of airway obstruction. [b] Centers may vary regarding which interventions are available. NG indicates nasogastric; VFSS, video fluoroscopic swallow study; GER, gastroesophageal reflux; G, gastrostomy; CT, computed tomography.

Several management protocols have been presented in the literature; however, no consensus about indications, efficacy, or risks has been reached.[6,62,100] Cole et al[101] suggested a unique classification system for RS based on functional parameters: severity of airway obstruction, breathing, and feeding difficulties. Care and caution must be exercised when interpreting recommendations for the whole group, because morphologic phenotype, airway physiology, and severity of RS vary.

Current treatment recommendations are constantly evolving, and a common theme is present: use the least invasive and most effective interventions to achieve improved breathing and feeding. Customized care can be achieved when considering the child holistically in the context of breathing (cyanosis, desaturation events, CO_2 retention), feeding (oral feeding, gastric tube supplementation), underlying diagnosis or syndrome, and their home and family (prolonged hospitalization, home care abilities). Over the past 10 years, our center has had the opportunity to treat nearly 200 children born with RS, which has led to the management scheme that we propose in Figure 7. We are systematically reviewing phenotype and outcomes in this cohort of children and hope to offer an enriched understanding of this population in the near future. Although we hope that this review will serve as a reference for providers who are caring for infants with RS, as science advances, surgical techniques improve,

and we better understand subpopulations of children born with RS, our management and protocols will evolve.

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